Research Techniques Made Simple

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Research Techniques Made Simple: Transepidermal Water Loss Measurement as a Research Tool

Short title: TEWL as a research tool

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Abbreviations:

TEWL- transepidermal water loss

AD- atopic dermatitis

SC- stratum corneum

FLG- filaggrin gene

ABSTRACT

Transepidermal water loss (TEWL) is the most widely used objective measurement for assessing the barrier function of skin in healthy individuals but also patients with skin diseases that are associated with skin barrier dysfunction, such as atopic dermatitis (AD). TEWL is the quantity of condensed water that diffuses across a fixed area of stratum corneum (SC) to the skin surface per unit time. The water evaporating from the skin is measured using a probe that is placed in contact with the skin surface and contains sensors that detect changes in water vapour density. TEWL can be measured using an open-chamber, unventilated-chamber or condenser-chamber device. It is a sensitive measure that is affected by properties of the surrounding microclimate such as environmental humidity, temperature, and airflow and should be measured under controlled conditions. TEWL varies significantly across different anatomical sites and also depends on sweat gland activity, skin temperature, and corneocyte properties. Here we describe how to optimally use TEWL measurements as a skin research tool *in vivo* and *in vitro*.

INTRODUCTION

The outer layer of the epidermis, the stratum corneum (SC), contributes to skin barrier properties and has many protective functions (Elias 2008), including contribution to the control of transcutaneous water loss. The movement of water across the SC is primarily controlled by flattened corneocytes surrounded by hydrophobic bilamellar lipids including ceramides, cholesterol, and free fatty acids. The permeability barrier function of the skin is critical and its impairment leads to downstream signals that aim to restore barrier homeostasis.

Transepidermal water loss (TEWL) measurement is the most widely used objective measurement for assessing the barrier function of the skin (Fluhr et al. 2006). TEWL measures the quantity of water lost from inside the body by diffusion across the SC. Skin barrier dysfunction results in increased TEWL. Skin diseases in which the skin barrier is disturbed, such as atopic dermatitis (AD), contact dermatitis, psoriasis, and ichthyoses, are associated with elevated TEWL.

TEWL as a measure of skin water barrier status has been validated in both humans and mice by correlating TEWL with absolute water loss determined gravimetrically (Fluhr et al. 2006). In addition to gauging water barrier function, *in vivo* TEWL measurements consistently correlate with the percutaneous absorption of topically applied compounds (Levin and Maibach 2005). As such, TEWL measurements can be seen as an indirect measure of skin permeability (both inside to outside and outside to inside), which is a function of skin barrier status. A stronger skin barrier, characterised by larger surface corneocytes, an increased number of corneocyte layers (increased path length across the SC), and/or improved inter-corneocyte lamellar lipid matrices are linked to reduced TEWL (Damien and Boncheva

2010). The molecular organization of the SC extracellular lipid matrix into a highly ordered lamellar bilayer structure is an important determinant of TEWL (Elias 2008). The proportion of SC composed of alpha-phase lipid bilayers inversely correlates with TEWL. Changes in the lipid matrix structure induced by environmental factors such as temperature and humidity may therefore be responsible for the differences in TEWL observed under these conditions (Damien and Boncheva 2010).

TEWL MEASUREMENT

TEWL is not measured directly, but inferred from measuring the change (or flux) in water vapour density at the skin surface compared with a point further away from the skin ((Nilsson 1977). If water loss across the SC were zero, then the humidity in the air adjacent to the skin surface would be the same as ambient humidity. As water loss across the SC increases, the humidity next to the skin surface rises above ambient humidity. This creates a humidity gradient above the skin surface that is proportional to the SC water loss (Imhof et al. 2009). Water vapour density measurements are taken over a fixed area of SC in a fixed time period, and the units for TEWL are stated as grams of water per square metre per hour ($g\ m^{-2}\ h^{-1}$).

TEWL can be measured using an open-chamber device, an unventilated-chamber device or a condenser-chamber device. Because of the sensitivity and variability in measurement of TEWL, usually three or more readings are taken in order to calculate a mean value.

TEWL DEVICES

Open-chamber devices consist of a hollow cylinder that is placed in contact with the skin (Nilsson 1977). Water vapour from the skin surface diffuses through the chamber and out into the ambient atmosphere. The humidity gradient is calculated from temperature and relative humidity readings from two sensors that are fixed at different distances from the skin surface (Figure 1a). An advantage of open-chamber devices is that they do not occlude the skin and therefore leave the cutaneous microclimate relatively undisturbed. One of their major limitations, however, is that they are vulnerable to environmental influences, such as disturbance from ambient air movements.

Unventilated-chamber devices consist of a chamber with a closed upper end, which protects from ambient air movement disturbances. Water vapour from the skin surface collects in the chamber causing the humidity to rise with time. Sensors in the chamber measure the rate of increase in relative humidity (Figure 1b). This method requires the chamber to be lifted from the skin after every reading to allow the accumulated water vapour to escape. These devices therefore cannot be used for continuous TEWL measurement.

The more recently developed condenser-chamber device has become increasingly used, as it provides a dynamic reading of the transcutaneous water loss (Imhof et al. 2009). The upper end of the chamber is closed by a condenser that is cooled below the freezing point of water. The condenser removes water vapour from the chamber, enabling continuous measurements to be made without the need to interrupt the measurement to allow the water vapour to escape. The condenser also controls the microclimate within the chamber by protecting from ambient air movement and controlling the humidity. The water vapour density is measured in a similar way to open chamber devices by separately spaced sensors in the chamber (Figure 1c).

A number of studies have compared the performance of different TEWL devices and find that results show good correlation (Fluhr et al. 2006; Farahmand et al. 2009). However, a small comparative study of an open-chamber system with an unventilated-chamber system and a condenser-chamber system found that the condenser-chamber system was the only device that could detect the effect of tape-stripping on TEWL and the only device that could discriminate between the effects of moisturiser and petrolatum on skin barrier integrity (Farahmand et al. 2009), suggesting that the condenser-chamber method gives greater sensitivity.

FACTORS AFFECTING TEWL

TEWL has been shown to vary significantly at different anatomical sites within an individual (Kottner et al. 2013). TEWL is high at the palms, soles, axillae and forehead and low at the calf and forearm. The increased TEWL at sites such as the palms and soles is linked to the low sebaceous lipid content at these sites (Brancaleon et al. 2001). Regional differences in TEWL may also be due to differences in sweat gland activity, occlusion, skin temperature, thickness, and microvasculature as well as corneocyte size, maturity, and shedding. In adults, some studies suggest that TEWL decreases with age but others have found no association between TEWL and age (Kottner et al. 2013; Zouboulis et al. 2018). Some studies have found TEWL differences in different ethnic groups. For instance, TEWL is higher in black and Asian skin compared to Caucasian skin (Kompaore et al. 1993). Skin care practices also affect TEWL. Detergents such as sodium lauryl sulfate can damage the skin barrier and lead to increased TEWL, whereas emollients transiently occlude the skin and reduce TEWL (Danby et al. 2016). Skin surface temperature and sweating additionally alter TEWL (Pinnagoda et al. 1990). Studies have also shown seasonal variation in TEWL and that TEWL is affected by circadian rhythm and sun exposure (Le Fur et al. 2001; Liu et al. 2010).

TEWL MEASUREMENT *IN VIVO*

Guidelines have been developed to help control external factors affecting TEWL in research studies and achieve consistency and accuracy (Pinnagoda et al. 1990; Rogiers and Group 2001). The selection of the skin area to be tested is important and the volar forearm is the site used most often for dermatological studies. There should be an interval of at least 12 hours between application of topical skin products and TEWL measurement and at least 2 hours between skin washing and TEWL measurement. A room of temperature 18-21°C and relative humidity 40-60% should be used and direct light avoided. Subjects should acclimatize to the environment for 20-30 minutes before TEWL measurement. TEWL measurements should ideally be taken at the same time of day, during the same season and avoiding the summer months.

Calibration of TEWL instruments is essential and depends on the device and manufacturer (Pinnagoda et al. 1990; Imhof et al. 2009). Due to the differences in TEWL measurement devices and study designs, there is a lack of consensus regarding reference TEWL values. It is therefore recommended that baseline TEWL measurements are recorded and that results are interpreted as a relative change (Rogiers and Group 2001).

In addition to the use of basal TEWL to assess the undisturbed permeability of the skin barrier, TEWL measurements conducted in conjunction with controlled skin barrier perturbation by tape-stripping is used to measure skin barrier integrity (Danby et al. 2011). Tape-stripping is a procedure where the uppermost layers of corneocytes are peeled away from the surface using standardized adhesive discs, such as D-Squame discs (CuDerm, TX).

Where the skin displays reduced structural integrity, tape-stripping removes more corneocytes, leading to a more rapid disruption of the skin barrier and consequently a sharper increase in TEWL with each consecutive stripping. Initially, healthy skin is fairly insensitive to tape-stripping, demonstrating the capacity of the skin to withstand mild perturbation. Disrupted skin and skin with a low structural integrity exhibit greater changes in TEWL underpinning the increased sensitivity of the technique. The area under the curve for TEWL measurements made over a defined number of tape strippings can be used to reflect the overall integrity of the SC (Figure 2). Quantifying the amount of protein removed by each tape strip disc can similarly be used to reflect the cohesiveness of the SC (Danby et al. 2016). Combining both the TEWL and protein data can be used to estimate the thickness of the SC by utilizing Fick's first law of diffusion (Bashir et al. 2001).

The measurement of skin barrier recovery rates after barrier impairment can reveal skin barrier differences that are not seen with basal TEWL measurement alone. For instance, ageing and stress lead to delayed skin barrier recovery whereas darkly pigmented skin, independent of race, recovers more quickly after tape stripping than lightly pigmented skin (Ghadially et al. 1995; Reed et al. 1995; Muizzuddin et al. 2003). Barrier recovery kinetics can also be used to assess response to topical treatments and to identify the metabolic processes that maintain a functioning skin barrier (Feingold 2009).

TEWL MEASUREMENT *IN VITRO*

TEWL has also been used as a quantitative parameter to assess skin barrier integrity and function in explanted skin (Sundaram et al. 2016; Döge et al. 2017; Zhang et al. 2018), skin

barrier formation in cultured skin models (Nolte et al. 1993) and epidermal models (Hatano et al. 2005; Kuntsche et al. 2008) *in vitro*.

TEWL may be measured on cultured samples directly (https://www.biox.biz/Products/ProductDetails.php), or after mounting in a Franz cell (http://www.courage-khazaka.de/index.php/en/products/scientific/382-tewitro-e) or with adaptation to allow multiple wells to be measured simultaneously (http://www.courage-khazaka.de/index.php/en/products/scientific/382-tewitro-e). TEWL measurement has been shown to directly correlate with the measurement of tritiated water flux, while being a safer and more user-friendly measurement (Elmahjoubi et al. 2009).

One advantage of TEWL measurement *in vitro* is that it is less sensitive to the variable of water loss by sweating that occurs *in vivo*, but repeated measurements show variation as the sample equilibrates to ambient temperature and humidity outside the tissue culture incubator, so equilibration time should be standardised across replicate experiments.

The absolute TEWL measurement shows variability between replicate experiments and the different models give different TEWL measurements (Figure 3), reflecting in part the different distances between water source (media and/or dermis) and the epidermal surface. Direct comparisons between experimental measurements are therefore not appropriate and it is important to include within-experiment controls for comparison.

CLINICAL APPLICATIONS OF TEWL MEASUREMENT

Skin barrier dysfunction and increased TEWL are major pathologic features of AD (Elias 2008; Flohr et al. 2010) . TEWL is used as a research tool to objectively assess skin barrier

function, and it can be robustly correlated with the severity of AD and response to treatment, leading to the inclusion of the parameter in some AD severity scores (Pinnagoda et al. 1990; Rogiers and Group 2001; Chamlin et al. 2002; Sugarman et al. 2003) . Filaggrin is a key component of the epidermal skin barrier and up to 50% of patients with moderate-severe AD are heterozygous for one of the filaggrin gene (*FLG*) loss-of-function mutations (Baurecht et al. 2007) . Studies have shown that at birth, there is no difference in TEWL between *FLG* mutation and *FLG* wild-type groups (Kelleher et al. 2015; Horimukai et al. 2016). However at 2 months, 3 months, and 6 months of age, those carrying a *FLG* mutation have a significantly higher TEWL than those without (Flohr et al. 2010; Kelleher et al. 2015). Importantly, TEWL was found to be elevated in infants with *FLG* null mutations even without clinical AD, suggesting that skin barrier impairment may precede the clinical manifestation of AD. Kelleher et al and Horimukai et al have demonstrated that TEWL measured during the first days of life can predict the development of AD in infancy, independent of *FLG* status. These findings suggest that TEWL could potentially be used to identify neonates at increased risk of AD and help to guide prevention strategies, for instance with regular emollient application.

CONCLUSIONS

TEWL is a research tool that enables objective and non-invasive measurement of one aspect of skin barrier function in dermatological research. TEWL elevation is a hallmark of AD and may precede clinical manifestation of the disease suggesting that TEWL measurement may be useful in guiding AD prevention strategies.

SUMMARY POINTS

- TEWL measurement is used to objectively assess the barrier function of the skin *in vivo* and *in vitro*.
- Skin diseases in which the skin barrier is disturbed, such as atopic dermatitis (AD), contact dermatitis, and psoriasis, are associated with elevated TEWL.
- TEWL can be measured using an open-chamber device, an unventilated-chamber device, or a condenser-chamber device.
- TEWL is affected by properties of the surrounding microclimate such as environmental humidity, temperature, and airflow, and should be measured under controlled conditions.

MULTIPLE CHOICE QUESTIONS

1. How is TEWL measured?

A. By measuring the volume of water on the surface of the skin

B. By measuring absolute water loss from the skin gravimetrically

C. By measuring relative humidity and temperature at the skin surface to calculate the change in water vapour density

D. By measuring evaporation of water from the skin to the atmosphere

2. What advantages do condenser-chamber TEWL devices have over unventilated and open-chamber devices?

A. Water can diffuse out of the chamber into the atmosphere.

B. Continuous TEWL measurements can be made and disturbance from ambient air movements is minimised.

C. The chamber is closed allowing water vapour to accumulate in the chamber.

D. Individual TEWL measurements can be made faster.

3. What are the suggested conditions for TEWL measurement?

A. Room temperature 18-21°C, relative humidity 40-60%, in direct light, and subjects should acclimatize to the environment for 20-30 minutes before TEWL measurement.

B. Room temperature 18-21°C, relative humidity 20-30%, avoid direct light, and subjects should acclimatize to the environment for 20-30 minutes before TEWL measurement.

C. Room temperature 18-21°C, relative humidity 20-30%, avoid direct light, and take measurement as soon as subject enters the testing environment.

D. Room temperature 18-21°C, relative humidity 40-60%, avoid direct light, and subjects should acclimatize to the environment for 20-30 minutes before TEWL measurement.

4. Which body regions have the highest TEWL?

A. Palms, soles, axillae, and forehead

B. Calves and forearms

C. Antecubital fossae

D. Abdomen, chest, and back

5. Which statement is true regarding TEWL in AD?

A. At 3 months of age, *FLG* mutation carrying infants do not have increased TEWL.

B. TEWL is increased at birth in *FLG* mutation carrying neonates compared to *FLG* wild-type neonates.

C. TEWL is not a parameter in any AD severity scores

D. TEWL measured during the first days of life can predict the development of AD in infancy.

ANSWERS

1. How is TEWL measured?

A. By measuring the volume of water on the surface of the skin

B. By measuring absolute water loss from the skin gravimetrically

C. By measuring relative humidity and temperature at the skin surface to calculate the change in water vapour density

Explanation:

As water loss across the SC increases, the humidity next to the skin surface rises and creates a humidity gradient that is proportional to the SC water loss. TEWL is inferred from measuring the change (or flux) in water vapour density at the skin surface compared with a point further away from the skin.

D. By measuring evaporation of water from the skin to the atmosphere

2. What advantages do condenser-chamber TEWL devices have over unventilated and open-chamber devices?

A. Water can diffuse out of the chamber into the atmosphere.

B. Continuous TEWL measurements can be made and disturbance from ambient air movements is minimised.

Explanation:

Condenser-chamber TEWL devices are closed by a condenser that is cooled below the freezing point of water. The condenser removes water vapour from the chamber, enabling continuous measurements to be made without the need to interrupt the measurement to allow the water vapour to escape. The condenser also controls the microclimate within the chamber by protecting from ambient air movement and controlling the humidity

C. The chamber is closed allowing water vapour to accumulate in the chamber.

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C. Room temperature 18-21°C, relative humidity 20-30%, avoid direct light, and take measurement as soon as subject enters the testing environment.

D. Room temperature 18-21°C, relative humidity 40-60%, avoid direct light, and subjects should acclimatize to the environment for 20-30 minutes before TEWL measurement.

Explanation:

Ambient temperature, humidity and light exposure have all be shown to affect TEWL measurement. Consensus guidelines suggest controlling these factors to achieve consistency and accuracy in TEWL measurement.

4. Which body regions have the highest TEWL?

A. Palms, soles, axillae, and forehead

Explanation:

Studies have found TEWL is highest at the palms, soles, axillae and forehead. The increased TEWL at sites such as the palms and soles is linked to the low sebaceous lipid content at these sites (Brancaleon et al. 2001). Regional differences in TEWL may also be due to differences in sweat gland activity, occlusion, skin temperature, thickness, and microvasculature as well as corneocyte size, maturity, and shedding.

B. Calves and forearms

C. Antecubital fossae

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B. TEWL is increased at birth in *FLG* mutation carrying neonates compared to *FLG* wild-type neonates.

C. TEWL is not a parameter in any AD severity scores

D. TEWL measured during the first days of life can predict the development of AD in infancy.

Explanation:

Kelleher et al and Horimukai et al showed that TEWL measured during the first days of life can predict the development of AD in infancy, independent of *FLG* status. These findings suggest that TEWL could potentially be used to identify neonates at increased risk of AD and help to guide prevention strategies, for instance with regular emollient application.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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FIGURE LEGENDS

Figure 1. TEWL devices. (a) Open-chamber TEWL device. A hollow cylinder is placed in contact with the skin and water vapour diffuses through the open-chamber. Spatially separated temperature and relative humidity sensors detect the humidity gradient. (b) Unventilated-chamber TEWL device. The upper end of the chamber is closed resulting in water vapour collecting in the chamber. The temperature and relative humidity sensors detect the rate of increase of relative humidity. (c) Condenser-chamber TEWL device. The upper end of the chamber is closed by a condenser that removes water vapour from the chamber enabling continuous TEWL measurements to be recorded. Water vapour density is measured by sensors in the chamber and condenser.

Figure 2. TEWL measurement in conjunction with controlled skin barrier perturbation by tape-stripping is used to measure skin barrier integrity in AD research. The area under the curve for TEWL measurements made over a defined number of tape strippings can be used to reflect the overall integrity of the SC.

Figure 3. *In-vitro* TEWL measurement from isolated human epidermis and rat epidermal keratinocyte organotypic cell culture epidermis (ROC) was used to determine the occlusive

properties of lipid nanoparticle formulations (MCT, D116, CM/CN, GMO) (n = 3-4) (reprinted from Kuntsche et al. 2008).

FIGURE 1

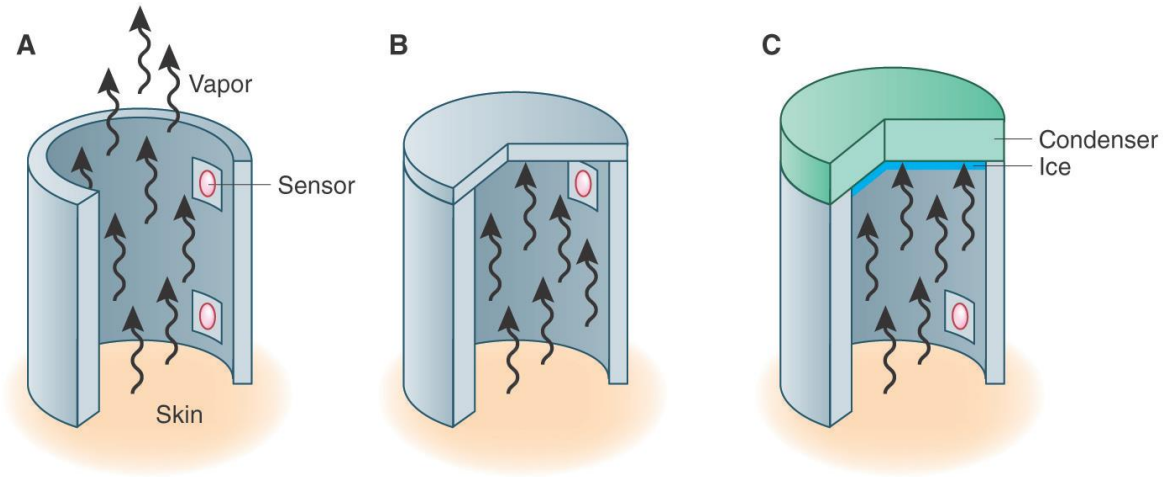


FIGURE 2

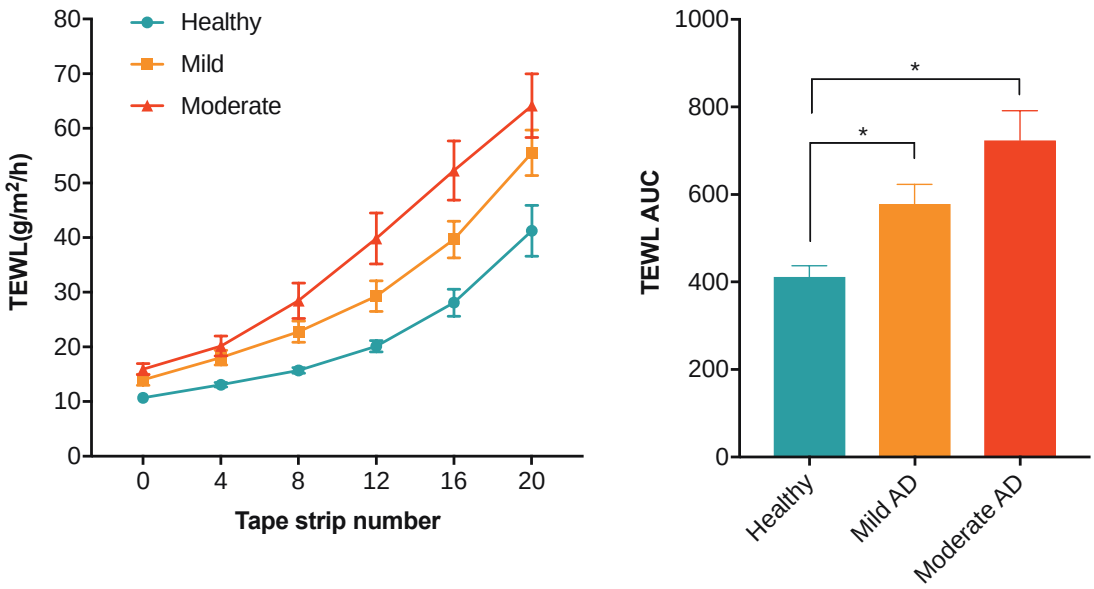
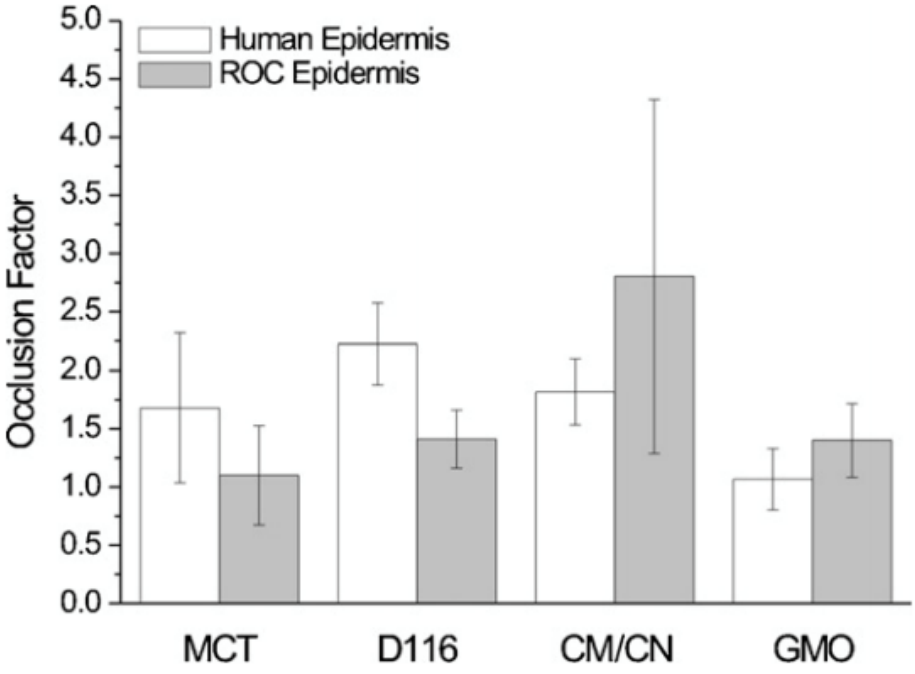


FIGURE 3

579


Human Epidermis
ROC Epidermis
Occlusion Factor
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
MCT
D116
CM/CN
GMO

580